PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of

Noboru YAMAJI, et al.

Appln. No.: 10/525,015

Confirmation No.: 5025

Filed: February 17, 2005

Docket No: Q86324

Group Art Unit: 1654

Examiner: Andrew D. KOSAR

For: AN AGENT FOR INHIBITING ARTICULAR CARTILAGE EXTRACELLULAR MATRIX DEGRADATION

AMENDED APPEAL BRIEF UNDER 37 C.F.R. § 41.37

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the provisions of 37 C.F.R. § 41.37, Appellant submits the following:

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I. REAL PARTY IN INTEREST

The real party in interest is Astellas Pharma Inc.

II. RELATED APPEALS AND INTERFERENCES

Appellants, Appellants' legal representative and the Assignee of this application are not aware of any other appeals or interferences which may be related to, directly affect or be affected by, or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 18-21 are pending in the application.

Claims 1-17 have been canceled.

Claims 18-21 are rejected.

This is an appeal from the Examiner's rejection of claims 18-21 under 35 U.S.C. § 102(b) over Watkins (WO 02/30879 A2).

IV. STATUS OF AMENDMENTS

The Amendment submitted on August 6, 2008 is the last response submitted with amendments to the claims of the application. The Amendment filed on August 6, 2008 was entered according to the Advisory Action mailed August 19, 2008.

There are no outstanding amendments to the claims or to the specification in the present application.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

The present invention relates to a method for treating osteoarthritis caused by articular cartilage extracellular matrix degradation.

Independent claim 18 of the present application recites a method for treating osteoarthritis caused by articular cartilage extracellular matrix degradation, which comprises administering a therapeutically effective amount of a histone deactylase-inhibiting compound to a patient in need thereof. See specification page 10, lines 16-23 and page 11, lines 8-12.

Claims 19-21 ultimately depend from claim 18.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 18-21 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Watkins (WO 02/30879 A2).

VII. ARGUMENT

The rejection of claims 18-21 under 35 U.S.C. § 102(b) based on Watkins should be reversed because Watkins does not contain an enabling disclosure of the treatment of osteoarthritis; and therefore the present invention is not anticipated.

The Examiner relies on Watkins as teaching that HDAC inhibitors are well known for treating osteoarthritis.

Appellants respectfully traverse the rejection and submit that Watkins is primarily directed to inhibition of proliferative conditions such as cancer and psoriasis. Watkins only mentions osteoarthritis as a disease or condition for which the disclosed HDAC inhibitors might be useful, but it does not teach a specific working example where an HDAC inhibitor is administered to a subject actually having osteoarthritis. Thus, Watkins does not identically disclose all elements of the present claims and for at least this reason does not anticipate the present claims.

Additionally, the disclosure of Watkins et al is not enabling as to a method of treatment of osteoarthritis when taken in view of the knowledge and skill available and the state of the art. "A reference contains an 'enabling disclosure' if the public was in possession of the claimed invention before the date of invention. 'Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention.' *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985)." See MPEP §2121.01. The disclosure in an assertedly anticipating reference must

provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation. *Id.*

At pages 110-111, Watkins et al states that inflammatory diseases such as osteoarthritis and rheumatoid arthritis are conditions which are known to be mediated by HDAC or are known to be treated by HDAC inhibitors. However, this statement is contrary to the knowledge and skill in the art with respect to treatment of osteoarthritis and cannot serve as an enabling disclosure.

Specifically, at pages 110-111, Watkins discloses:

> The compounds of the present invention may also be used in the treatment of conditions which are known to be mediated by HDAC, or which are known to be treated by HDAC inhibitors (such as, e.g., trichostatin A). Examples of such conditions include, but are not limited to the following:
> Cancer (see, e.g., Vigushin et al., 2001).
> Inflammatory disease (e.g., osteoarthritis, rheumatoid arthritis) (see, e.g., Dangond et al., 1998; Takahashi et al., 1996).

The mere disclosure of Watkins at pages 110-11 relied on by the Examiner is not sufficiently enabling for the treatment of osteoarthritis for purposes of anticipation under 35 U.S.C. § 102 since it does not provide any examples, direction or guidance for use of a specific HDAC inhibitor agent in the treatment of osteoarthritis. Additionally, the references cited by Watkins in support of the assertion that HDAC inhibitors were known to treat inflammatory diseases such as osteoarthritis and rheumatic arthritis do not even mention these conditions and thus do not support the assertion made by Watkins.

Specifically, Watkins is not enabling for the use of HDAC inhibitor compounds in the treatment of osteoarthritis. Watkins discloses carbamic acid compounds and teaches that the compounds are useful as HDAC inhibitors, in particular, useful to inhibit proliferative conditions, such as cancer and psoriasis. The biological activity concretely disclosed in Watkins is merely a finding of "the ability to inhibit deacetylase activity and to inhibit cell proliferation" (cf. pages 230-247). Although Watkins describes reasons for usefulness for inhibiting proliferative conditions, such as cancer and psoriasis, in detail, the description about other uses is limited to the description at pages 110-111. At page 110, lines 15-18, it is described, "The compounds of the present invention may also be used in the treatment of conditions which are known to be mediated by HDAC, or which are known to be treated by HDAC inhibitors". But Watkins does not provide any additional guidance as to how the compounds can be used to treat osteoarthritis other than the reference to Dangond et al and Takahashi et al (of record, submitted as Attachments 1 and 2 to the Amendment filed January 31, 2008) and these references do not mention osteoarthritis.

Dangond et al and Takahashi et al do not have any disclosure relating to the use of the compounds described therein in the treatment of osteoarthritis and inflammatory disease. Dangond et al describes that "HDACs suggests they play a fundamental role in multiple and complex cellular pathways of immune system regulation" and Takahashi et al discloses that Trichostatin A inhibits IL-2 gene expression and has immunosuppressive activity and proliferation inhibiting activity. Thus, it is apparent that these disclosures do not establish a nexus between HDACs and osteoarthritis. Appellants have pointed out that osteoarthritis is not a

disease relating to the immune system. Osteoarthritis is a disease where degradation of extracellular matrix constituted from collagen and proteoglycan occurs. However, as is apparent from the description of classification of autoimmune diseases (refer to Table 2-2, page 29 of Reference Document 3, of record, submitted with the Amendment filed November 27, 2006) and its mechanism of action (refer to Fig. 4, page 32 of Reference Document 4, of record, submitted with the Amendment filed November 27, 2006), osteoarthritis is not an autoimmune disease.

Also, of all the references of record in the present application, there is no reference which shows that osteoarthritis is "known to be mediated by HDAC" or "known to be treated by HDAC inhibitors". Accordingly, Watkins does not show enablement for the use of HDAC inhibitor compound in the treatment of osteoarthritis.

The Examiner has not pointed to any other references in support of his position that Watkins is enabling for the treatment of osteoarthritis. In the Advisory Action dated July 3, 2008, the Examiner states that one need not look beyond the disclosure of Watkins since Watkins states that it is well known to treat osteoarthritis with HDAC inhibitors. More specifically, the Examiner states "Watkins provides the disease, the statement it can be treated with HDACi and provides a myriad of HDACi's [*sic*] to use". However, this is not the standard for determining whether a reference is enabling. As noted above, a reference contains an enabling disclosure if the public was in possession of the claimed invention before the date of invention. Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention. See MPEP §2121.01 citing *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985). In this

case, the description in Watkins is insufficient and the knowledge and remainder of the prior art does not support the description in the Watkins reference that it was well known that HDACi's could be used for the treatment of osteoarthritis.

As explained above, Dangond et al and Takahashi et al, which are cited in Watkins as references for inflammatory disease (e.g., osteoarthritis, rheumatoid arthritis), describe that the immunosuppressive activity is the base. Accordingly, each of these references indicates that the HDAC inhibitor acts on rheumatoid arthritis through immunosuppressive activity.

On the other hand, as described above, osteoarthritis is neither an autoimmune disease nor a disease in which CD154, IL-10, and INF-gamma participate. Accordingly, considering the functional mechanism of the HDAC inhibitor disclosed in the references, it is quite apparent that the use for osteoarthritis would be distinguished from the use for rheumatoid arthritis by those of ordinary skill in the art.

Moreover, even if Watkins could be considered as describing osteoarthritis and rheumatoid arthritis in parallel, one skilled in the art who understood the contents of all of these references would not consider that the HDAC inhibitor can act on osteoarthritis through its immunosuppressive activity and rather would doubt its enablement. Thus, one skilled in the art would not consider to apply the HDAC inhibitor to osteoarthritis similar to rheumatoid arthritis.

In view of the above, Appellants respectfully submit that the totality of the evidence provided on the record must be considered, which establishes that Watkins is not an enabling reference and does not disclose, teach or suggest the present invention of treating osteoarthritis caused by articular cartilage extracellular matrix degradation, which comprises administering a

therapeutically effective amount of a histone deacetylase-inhibiting compound to a patient in need thereof as recited in independent claim 18. The ultimate determination of patentability is based on the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence. See MPEP § 2142 citing *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). The legal standard of "a preponderance of evidence" requires the evidence to be more convincing than the evidence which is offered in opposition to it. When an Applicant submits evidence, whether in the specification as originally filed or in reply to a rejection, the Examiner must reconsider the patentability of the claimed invention and the decision on patentability must be made based upon consideration of all the evidence, including the evidence submitted by the Examiner and the evidence submitted by the Applicant. A decision to make or maintain a rejection in the face of all the evidence must show that it was based on the totality of the evidence. Facts established by rebuttal evidence must be evaluated along with the facts on which the conclusion was reached, not against the conclusion itself. See MPEP § 2142 citing *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990).

In this case, Appellants have pointed out that: (1) Watkins does not provide a specific example wherein an HDAC inhibitor is used to treat osteoarthritis and does not provide an enabling disclosure for such a method of treatment; (2) the references referred to by Watkins in support of the statement that the method of treatment of osteoarthritis using HDACi's was well known do not even mention these conditions and thus do not support the assertion made by Watkins; (3) none of the other references of record indicate that osteoarthritis is "known to be

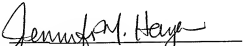
mediated by HDAC" or "known to be treated by HDAC inhibitors"; and (4) the Examiner has not pointed to any other references in support of his position that Watkins is enabling for the treatment of osteoarthritis.

On the other hand, the Examiner has made statements regarding the disclosure of Watkins which are contradicted by objective evidence of the knowledge and skill available in the art. Accordingly, the evidence presented by Appellants is more convincing than the mere statements of the Examiner. Thus, patentability of the present claims is supported by a preponderance of the evidence when the totality of the record is properly taken into consideration.

Accordingly, Appellants respectfully submit that the anticipation rejection should be reversed.

The USPTO is directed and authorized to charge the statutory fee (37 C.F.R. §41.37(a) and 1.17(c)) and all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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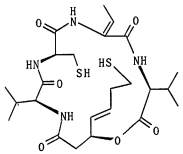
CLAIMS APPENDIX

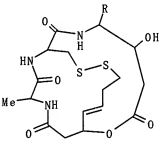
CLAIMS 18-21 ON APPEAL:

18. A method for treating osteoarthritis caused by articular cartilage extracellular matrix degradation, which comprises administering a therapeutically effective amount of a histone deacetylase-inhibiting compound to a patient in need thereof.

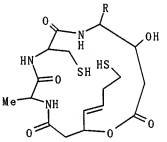
19. The method according to claim 18, wherein the histone deacetylase-inhibiting compound is selected from FK228, MS-27-275, Trichostatin A, NVP-LAQ824, SAHA, Apicidin, Phenylbutyrate, Valproic acid, Pivaloyloxymethyl butyrate, CI-994, Depudecin, Trapoxin, a CHAP, butyric acid and a depsipeptide compound represented by the following formula (I), a depsipeptide compound represented by the following general formula (II), and a depsipeptide compound represented by the following general formula (IIa):



(I)



(II)



(IIa)

wherein R represents an isopropyl group, a sec-butyl group, or an isobutyl group.

20. The method according to claim 19, wherein the histone deacetylase-inhibiting compound is selected from FK228, the depsipeptide compound represented by formula (I), the depsipeptide compound represented by formula (II), the depsipeptide compound represented by

formula (IIa), MS-27-275, Trichostatin A, NVP-LAQ824, SAHA, Apicidin, Phenylbutyrate, and Valproic acid.

21. The method according to claim 18, wherein the histone deacetylase-inhibiting compound is a compound whose histone deacetylase inhibitory activity (IC_{50} value) is a concentration of 100 μM or less measured by a histone deacetylase inhibition assay comprising:

(a) pre-incubating the histone deacetylase-inhibiting compound with [^{3}H] acetyl-histones in a solution containing PTT for 1 hour at room temperature,

(b) adding histone deacetylase to the solution of step (a) and incubating at room temperature for 2 hours, and

(c) measuring the released [^{3}H].

EVIDENCE APPENDIX:

Pursuant to 37 C.F.R. § 41.37(c)(1)(ix), submitted herewith are copies of any evidence submitted pursuant to 37 C.F.R. §§ 1.130, 1.131, or 1.132 or any other evidence entered by the Examiner and relied upon by Appellant in the appeal.

These documents have been submitted:

(1) Dangond et al., "Differential display cloning of HDAC3 cDNA from PHA-activated immune cells", 1998, Biochem. Biophys. Res. Commun., Vol 242, No.3, pp. 648-652 submitted as Attachment 1 with the Amendment filed January 31, 2008.

(2) Takahashi et al., "Selective Inhibition of IL-2 Gene Expression by Trichostatin A, a Potent Inhibitor of Mammalian Histone Deacetylase" 1996, J. Antibiot. (Tokyo), Vol. 49, No.5, pp. 453-457) submitted as Attachment 2 with the Amendment filed January 31, 2008.

(3) Partial English translation of New Integrated Medical Lectures, Classification of Autoimmune Diseases, submitted as Reference Document 3 with the Amendment filed November 27, 2006.

(4) Partial English translation of Orthopedic Surgery, No. 42, submitted as Reference Document 4 with the Amendment filed November 27, 2006.

RELATED PROCEEDINGS APPENDIX

Submitted herewith are copies of decisions rendered by a court or the Board in any proceeding identified about in Section II pursuant to 37 C.F.R. § 41.37(c)(1)(ii).

None